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ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Intratumoral delivery of tavokinogene telseplasmid yields systemic immune responses in metastatic melanoma patients

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Background: Interleukin 12 (IL-12) is a pivotal regulator of innate and adaptive immunity. We conducted a prospective open-label, phase II clinical trial of electroporated plasmid IL-12 in advanced melanoma patients (NCT 01502293).

Patients and methods: Patients with stage III/IV melanoma were treated intratumorally with plasmid encoding IL-12 (tavokinogene telseplasmid; tavo), 0.5 mg/ml followed by electroporation (six pulses, 1500 V/cm) on days 1, 5, and 8 every 90 days in the main study and additional patients were treated in two alternative schedule exploration cohorts. Correlative analyses for programmed death-ligand 1 (PD-L1), flow cytometry to assess changes in immune cell subsets, and analysis of immune-related gene expression were carried out on pre- and post-treatment samples from study patients, as well as from additional patients treated during exploration of additional dosing schedules beyond the pre-specified protocol dosing schedule. Response was measured by study-specific criteria to maximize detection of latent and potentially transient immune responses in patients with multiple skin lesions and toxicities were graded by the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

Results: The objective overall response rate was 35.7% in the main study (29.8% in all cohorts), with a complete response rate of 17.9% (10.6% in all cohorts). The median progression-free survival in the main study was 3.7 months while the median overall survival was not reached at a median follow up of 29.7 months. A total of 46% of patients in all cohorts with uninjected lesions experienced regression of at least one of these lesions and 25% had a net regression of all untreated lesions. Transcriptomic and immunohistochemistry analysis showed that immune activation and co-stimulatory transcripts were up-regulated but there was also increased adaptive immune resistance.

Conclusions: Intratumoral Tavo was well tolerated and led to systemic immune responses in advanced melanoma patients. While tumor regression and increased immune infiltration were observed in treated as well as untreated/distal lesions, adaptive immune resistance limited the response.

Key words: Immunotherapy, IL-12, Tavokinogene telseplasmid, intratumoral, melanoma, electroporation, cytokine

INTRODUCTION

The cytokine interleukin 12 (IL-12) occupies a unique niche in the cytokine repertoire bridging the innate and adaptive immune systems.[1] IL-12 is typically triggered upon pathogen-associated molecular pattern or danger-associated molecular pattern recognition and causes secretion of interferon-γ (IFN-γ) by T cells, natural killer (NK) cells, and dendritic cells (DCs), which in turn causes additional IL-12 production by immune cells. IL-12 causes T_H1 polarization, reduces regulatory T cells, and converts myeloid-derived suppressor cells to functional DCs. In addition, IL-12 (and IFN-γ) are crucial third signals sent by cross-presenting DC (cDC1) to naive CD8+ T cells, aiding their transformation into effector T cells.[2] Intravenous recombinant IL-12 (rIL-12) has shown clinical efficacy in solid tumor malignancies including renal cell cancer[3] and melanoma,[4] albeit with a high level of serious adverse events (AEs). Subcutaneous and intralesional recombinant cytokines have a lower toxicity, but also a much lower efficacy.[5]

In contrast to intralesional and systemic rIL-12, intratumoral injection of plasmid encoding IL-12 (Tavo) leads to sustained cytokine elaboration in the tumor microenvironment *in vivo*, with minimal systemic exposure. In the syngeneic B16 melanoma model, local IL-12 plasmid electroporation causes regression of both established local

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and distant (non-treated) lesions, while yielding immune memory to tumor rechallenge.[6–8] A phase I clinical trial of IL-12 plasmid electroporation established a biologically effective dose and demonstrated the safety of this approach, as well as its preliminary efficacy in increasing intratumoral IL-12 and IFN-γ, yielding sustained, global remissions in several patients after one cycle of therapy. We evaluated Tavo for efficacy and safety in an open-label, phase II trial.

METHODS

Study design

This was a prospective, multicenter, open-label, phase II trial (NCT01502293) evaluating the clinical efficacy and safety of Tavo in melanoma patients.

Patients

Eligible patients were required to be ≥18 years old with pathologically documented melanoma, with Eastern Cooperative Oncology Group (ECOG) performance status of 0—2, and an unresectable American Joint Committee on Cancer (AJCC) stage IIIB, IIIC, or IV A, B, or C, and two or more melanoma lesions accessible to electroporation. Any prior therapy was permitted. Any treatment-related toxicities resolved to grade 1 or better before study treatment.

Treatment

Tavo (IL-12 plasmid, 0.5 mg/ml) was administered on days 1, 5, and 8 of each 90-day cycle (Figure 1) by intratumoral injection at a dose volume of one-quarter of the calculated lesion volume (minimum = 0.1 ml).[9] Electroporation was carried out using six pulses of 1500 V/cm and a pulse width of 100 μs at 1-second intervals (ImmunoPulse, OncoSec Medical, Inc. San Diego, CA). Additional patients treated with the same plasmid dose but on different schedules (dose schedule exploration, supplementary Figure S1, available at *Annals of Oncology* online) were included in the translational and untreated lesion response analyses.

Efficacy assessment

Tumor lesions and tumor response were assessed by the investigator according to a modified version of RECIST version 1.0 that allowed inclusion of any number of skin lesions >0.3 cm at the largest diameter to be followed as target lesions, inclusion of latent responses, and assessment of the net tumor burden in the setting of new lesions. Progression-free survival was assessed as the time from the first day of study treatment until the time that the sum of the diameters of all measurable lesions increased by at least 30% from baseline. Additional information regarding response measures for treated and untreated lesions is provided in the supplementary Materials, available at *Annals of Oncology* online.

Safety evaluation

Safety was assessed by monitoring AEs, pain assessments, clinical laboratory tests, and vital signs. AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Translational medicine and statistical plan

See the supplementary Materials, available at *Annals of Oncology* online.

RESULTS

Baseline patient characteristics

For the main study, 38 patients were consented and 30 were eligible for the study and received at least one dose of treatment (Table 1). Of these, 28 patients were assessable for response (one withdrew before post-treatment assessment, one was deemed ineligible after initiation of treatment). Prior exposure to immunotherapy included 13 patients treated previously with systemic cytokines (high dose IL-2 or IFNα-2a), nine patients treated with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies and four patients (13.3%) treated with anti-programmed cell death protein 1 (PD-1) antibodies. In

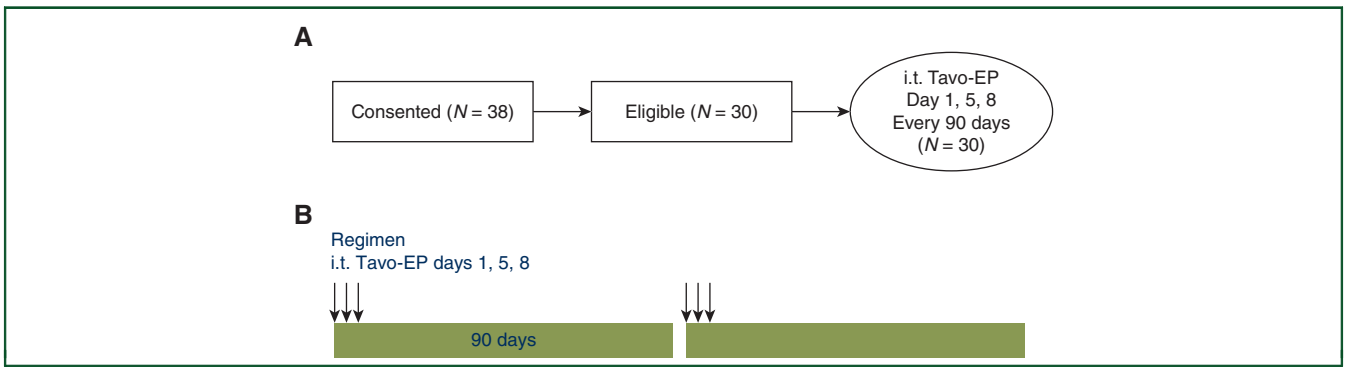

Figure 1. (A) CONSORT diagram with the screening and treatment assignments of patients consented to study. (B) Tavokinogene telseplasmid (0.5 mg/ml) was injected at a dose-volume of one-quarter of the calculated lesion volume. Patients were treated on days 1, 5, and 8 of every 90-day treatment cycle. Tumor response assessments were made every 90 days.
EP, electroporation; i.t., intratumoral.

Table 1. Patient demographics and patient history

Age	Mean (SD)	66.8 (10.19)
Sex	Male	16 (53.3%)
	Female	14 (46.7%)
ECOG PS	0	21 (70.0%)
	1	9 (30.0%)
Stage	IIIb	6 (20.0%)
	IIIc	13 (43.3%)
	IV M1a	8 (26.7%)
	IV M1b	3 (10.0%)
	IV M1c	0
BRAF status	Mutant	10 (33.3%)
	Wild-type	13 (43.3%)
	Unknown	7 (23.4%)
Prior therapy	Cytokine	13 (43.3%)
	CTLA-4	9 (26.7%)
	PD-1/PD-L1	4 (13.3%)
	Cytokine + CTLA-4	1 (3.3%)
	BRAF/MEK	3 (10%)
	Other	5 (16.7%)
Prior lines	0	10 (33.3%)
	1	10 (33.3%)
	2+	10 (33.3%)
		$N = 30$

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance status; SD, standard deviation.

addition, 24 patients were screened and 21 additional patients were treated in the schedule exploration cohorts (demographics are described in supplementary Table S1, available at *Annals of Oncology* online).

AEs

All treatment-emergent AEs (TEAEs) regardless of attribution observed in at least two patients and all grade 3 or higher TEAEs are described in Table 2. Transient procedural pain ($n = 24$, 80%) and injection site reactions were common. Constitutional symptoms were observed in a minority of patients including fatigue ($n = 5$, 16.7%), pyrexia ($n = 2$, 6.7%), and chills ($n = 2$, 6.7%). Grade 3 TEAEs were limited to transient procedural pain ($n = 1$, 3.3%) and a cerebrovascular accident that was determined to be unrelated to treatment on study. A patient in one of the schedule exploration cohorts also had grade 3, treatment-related cellulitis (supplementary Table S2, available at *Annals of Oncology* online).

Clinical response

The best overall response rate at any time point for Tavo treatment in the main study population (cohort A) was 35.7 % (waterfall plot, Figure 2A). Seven patients had disease progression before the first response assessment at 90 days and are represented as having a 100% change in tumor burden for graphic purposes. Responses included five complete responses and responses in patients with extensive in-transit/satellite metastases (Figure 2E and F). The clinical response rate was 26.7% in cohort B (4/15) and none of the four patients treated in cohort C responded. The best overall response rate for patients in all cohorts was

Table 2. All treatment-emergent adverse events observed in at least two patients and all grade 3 or higher adverse events

Category	Toxicity	Grade 1	Grade 2	≥ Grade 3	All grades
All		10 (33.3%)	15 (50.0%)	4 (13.3%)	29 (96.7%)
Gastrointestinal	Nausea	4 (13.3%)	1 (3.3%)	–	5 (16.7%)
	Vomiting	2 (6.7%)	2 (6.7%)	–	4 (13.3%)
	Diarrhea	1 (3.3%)	2 (6.7%)	–	3 (10.0%)
Constitutional	Fatigue	4 (13.3%)	1 (3.3%)	–	5 (16.7%)
	Injection site discoloration	4 (13.3%)	–	–	4 (13.3%)
	Injection site inflammation	3 (10.0%)	1 (3.3%)	–	4 (13.3%)
	Chills	2 (6.7%)	–	–	2 (6.7%)
	Injection site discharge	2 (6.7%)	–	–	2 (6.7%)
	Injection site erythema	2 (6.7%)	–	–	2 (6.7%)
	Edema peripheral	2 (6.7%)	–	–	2 (6.7%)
	Pain	–	2 (6.7%)	–	2 (6.7%)
	Pyrexia	2 (6.7%)	–	–	2 (6.7%)
Infectious	Cellulitis	–	2 (6.7%)	–	2 (6.7%)
Procedural	Procedural pain	23 (76.7%)	–	1 (3.3%)	24 (80.0%)
Musculoskeletal	Pain in extremity	4 (13.3%)	1 (3.3%)	–	5 (16.7%)
	Arthralgia	2 (6.7%)	1 (3.3%)	–	3 (10.0%)
	Muscle spasms	2 (6.7%)	–	–	2 (6.7%)
	Musculoskeletal stiffness	2 (6.7%)	–	–	2 (6.7%)
Neoplasms	Neoplasms NOS	–	2 (6.7%)	–	2 (6.7%)
Nervous system	Headache	4 (13.3%)	1 (3.3%)	–	5 (16.7%)
	Dizziness	2 (6.7%)	–	–	2 (6.7%)
	Cerebrovascular accident	–	–	1 (3.3%)	1 (3.3%)
Psychiatric	Anxiety	1 (3.3%)	2 (6.7%)	–	3 (10.0%)
Respiratory	Cough	1 (3.3%)	1 (3.3%)	–	2 (6.7%)
Cutaneous	Pruritus	2 (6.7%)	1 (3.3%)	–	3 (10.0%)
	Rash	3 (10.0%)	–	–	3 (10.0%)
	Ecchymosis	2 (6.7%)	–	–	2 (6.7%)
	Skin disorder	1 (3.3%)	1 (3.3%)	–	2 (6.7%)
Vascular	Lymphedema	2 (6.7%)	–	–	2 (6.7%)

NOS, not otherwise specified.
N = 30.

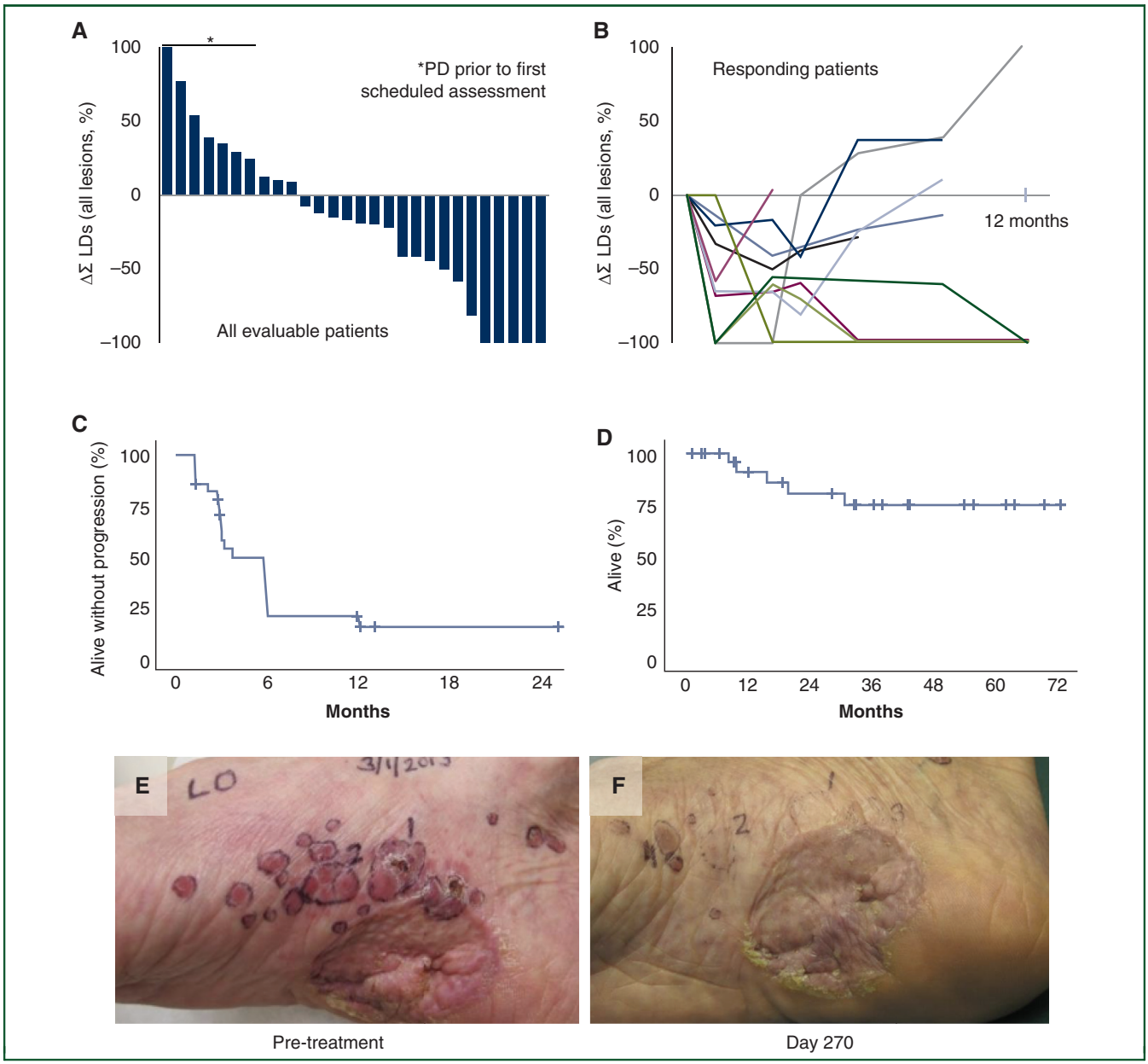

Figure 2. **(A) Best overall response in all assessable patients ($n = 28$) assessed as the sum of diameters of target lesions by a modified version of RECIST version 1.0 (* = disease progression due to progression of non-targets). (B) A spider plot demonstrating durables and transient responses in responding patients ($n = 8$). (C) Kaplan–Meier plots for progression-free survival (PFS) and (D) overall survival (OS). The median PFS was 3.7 months (95% confidence interval 0.6–6.9 months) and the median OS was not reached at a median follow-up of 29.7 months. (E) A patient with extensive satellite lesions before treatment demonstrates (F) complete regression of treated and untreated lesions by day 270.**

29.8% (supplementary Figure S2, available at *Annals of Oncology* online). Per-patient lesion and response data are presented in supplementary Table S3, available at *Annals of Oncology* online.

Adaptive resistance and response to checkpoint therapy

The median progression-free survival was 3.72 months [95% confidence interval (CI) 0.55–6.89], 3.2 months (95% CI 2.41–3.97), and 2.5 months (95% CI not defined) in cohorts A (main study), B, and C, respectively. The median overall survival was not reached in any cohort (Figure 2C and D, supplementary Figure S2B, available at *Annals of Oncology* online). Treatment with Tavo induced adaptive resistance as demonstrated by increases in programmed death-ligand 1 (PD-L1) expression by immunohistochemistry (Figure 3A). As a possible consequence, although durable responses were seen in four patients, transient responses were observed in six others (Figure 2B). In some patients, however, Tavo increased the total number of tumor infiltrating lymphocytes and the CD8:FoxP3 ratio suggesting an increase in the relative abundance of effector T cells versus regulatory cells (e.g. Figure 3C–E), and, in a retrospective analysis, six of eight patients progressing on Tavo responded to pembrolizumab immediately thereafter (Figure 3B, F–J).

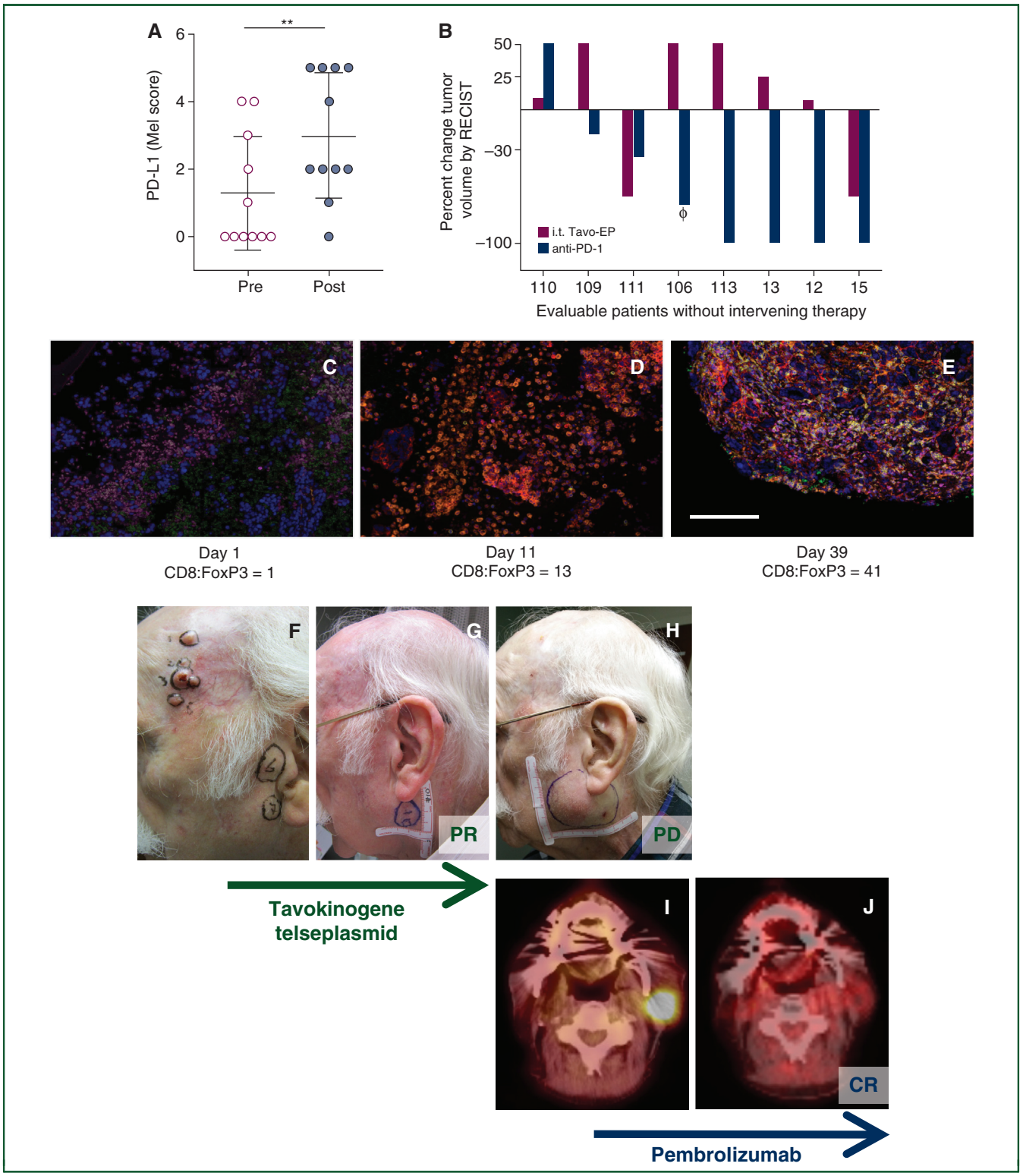

Figure 3. (A) Treatment with tavokinogene telseplasmid was associated with an increase in PD-L1 IHC scores suggesting induction of adaptive resistance. (B) Responses to Tavo and subsequent anti-PD-1 antibody therapy in 8 patients treated with Tavo followed immediately by an anti-PD1 antibody (ϕ denotes patient response assessed by FDG-PET). (C–E) Treatment with Tavo was associated with an increase in CD8+ cells and an increase in the CD8+:Foxp3+ cells in a responding patient. (F–J) A patient with a transient response to Tavo followed by a durable response to pembrolizumab by FDG-PET.

FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; IHC, immunohistochemistry; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PET, positron emission tomography.

Inflammatory gene expression

Tavo induced significant increases in multiple immune transcripts (Figure 4A), including modules associated with immune activation (Figure 4B), NK cell activity, antigen presentation and adaptive resistance (Figure 4C), as well as T cell trafficking (Figure 4D); all characteristic of an

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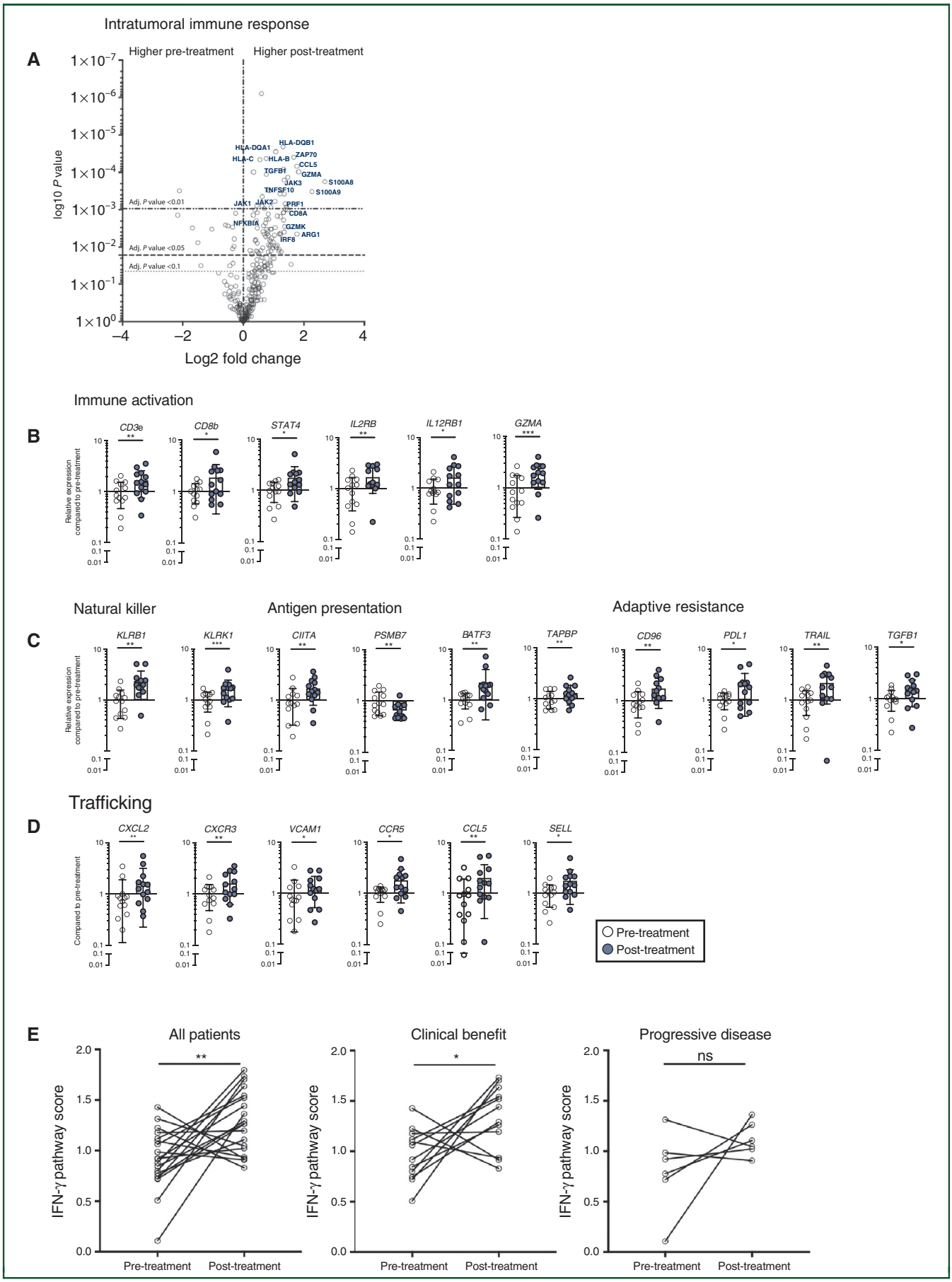
Intratumoral immune response
A
Higher pre-treatment
Higher post-treatment
log10 P value
Log2 fold change
Adj. P value <0.01
Adj. P value <0.05
Adj. P value <0.1
HLA-DQA1
HLA-DQB1
HLA-C
HLA-B
ZAP70
CCL5
TGFBI
GZMA
JAK3
S100A8
TNFSF10
S100A9
JAK1
JAK2
PRF1
CD8A
NFKBIA
GZMK
ARG1
IRF8
Immune activation
B
CD3e
CD8b
STAT4
IL2RB
IL12RB1
GZMA
Relative expression compared to pre-treatment
Natural killer
Antigen presentation
Adaptive resistance
C
KLRB1
KLRK1
CIITA
PSMB7
BATF3
TAPBP
CD96
PDL1
TRAIL
TGFB1
Trafficking
D
CXCL2
CXCR3
VCAM1
CCR5
CCL5
SELL
Compared to pre-treatment
Pre-treatment
Post-treatment
E
All patients
Clinical benefit
Progressive disease
ns
IFN-γ pathway score
Pre-treatment
Post-treatment

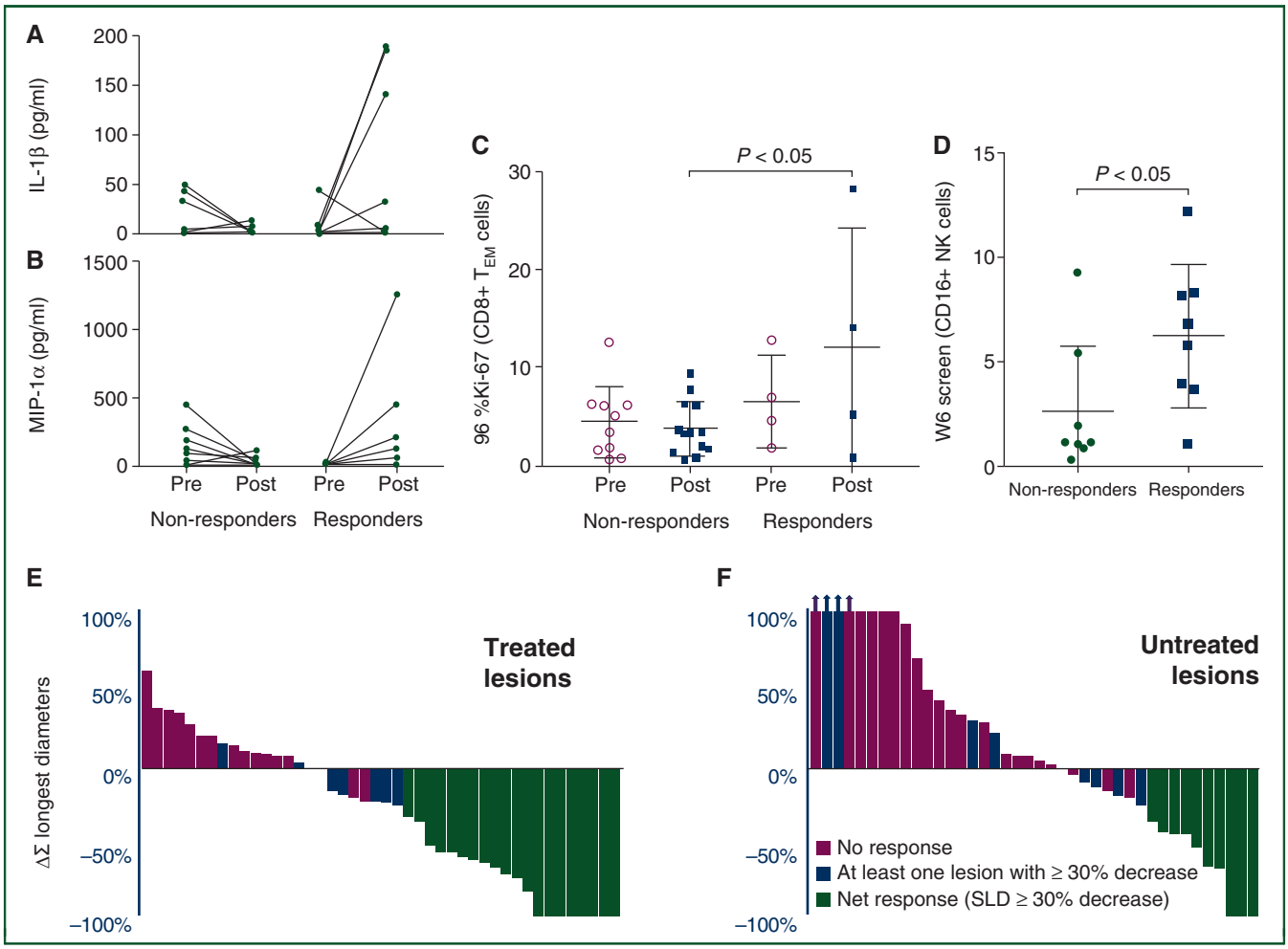

Figure 5. Signs of systemic immune activity after treatment with tavokinogene telseplasmid (Tavo). Tavo increased circulating levels of (A) IL-1β and (B) MIP-1α as well as (C) the proportion of proliferating effector T cells in the periphery in responding patients. (D) Tavo increased the frequency of NK cells in the periphery in the responding population. (E) Best overall response in treated and (F) untreated lesions as assessed as the sum of diameters of all lesions in each categories for patients treated in the main study and in the additional cohorts (B and C). Regression of at least one untreated lesions was observed in 46% of patients.
IL-1β, interleukin 1-beta; MIP-1α, macrophage inflammatory protein-1α.

antitumor immune response. Specific findings included increased expression of CD3E, CD8, STAT4, IL-2RB and IL-12RB1 as well as effector molecules such as GZMA, consistent with the known effect of IL-12 on T cell and NK cell activation.[1] A significant increase in transcripts associated with cross-presenting DCs[10] such as CIITA, BATF3, PSMB7 and TAPBP1[11] were also noted. Additionally, the chemokine receptor CXCR3, expressed on T_H1-polarized T cells, as well as chemokines and adhesion molecules were significantly increased. However, this global increase in genes associated with productive antitumor immunity was accompanied by increases in genes associated with adaptive resistance including CD274 (PD-L1), TRFB1 and TRAIL. IFN-γ gene expression increased overall in patients benefitting from treatment, but not in patients with progressive disease as the best treatment response (Figure 4E). Overall, these results suggest that Tavo induced NK cell and DC activation, recruitment, and activation of CD4+ T cell and CD8+ T cells, as well as the compensatory development of adaptive resistance.

Systemic immune response

We assessed systemic immune activity after treatment with Tavo. Analysis of serum inflammatory markers showed an increase in IL-1β and MIP-1α in responders but not in non-responders (Figure 5A and B). Systemic increases were seen in proliferating effector memory CD8+ T cells (Ki-67$^+$CCR7−CD45RA−, Figure 5C) and in circulating cytolytic

Figure 4. Tavokinogene telseplasmid-induced productive antitumor immune responses. (A) Volcano plot of both non-responding and responding patients based on transcriptional analysis of biopsies collected at screening and post-treatment. In particular, intratumoral expression of genes associated with (B) immune activation (C) natural killer (NK) cell activity, antigen presentation, adaptive resistance, and (D) T cell trafficking was increased after treatment. (E) Interferon-γ gene expression increased overall and in patients benefitting from treatment, but not in patients with progressive disease as the best treatment response (n = 28 including 14 patients with pre-/post-biopsy specimens).
IFN, interferon.

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NK cells ($CD56^{dim}CD16+$, Figure 5D) in responding but not in non-responding patients ($P < 0.05$).

For patients in the main study and expansion cohorts, responses in untreated lesions were common. In 40 patients with uninjected pre- and post-treatment tumor measurements available, the best overall response for untreated lesions was 25% ($n = 40$, Figure 5F) compared with a 43.8% response rate in treated lesions ($n = 45$ patients, Figure 5E). The per-lesion response rate for treated lesions was 62.7% (64/102) and for untreated lesions it was 17.4% (20/115).

DISCUSSION

Prior therapeutic approaches to rIL-12, including intralesional and systemic administration, have had limited efficacy due to transient exposures associated with intralesional therapy[12] and severe toxicity associated with systemic administration.[13] We previously described a phase I intratumoral dose-escalation pIL-12 electroporation trial demonstrating that a plasmid concentration of 0.5 mg/ml was well tolerated and showed clinical effectiveness with abscopal responses and systemic immune activation.[9] In the current report, we confirm these findings in a phase II expansion, demonstrating a 35.7% overall response rate in the main study and a 29.8% overall response rate in all cohorts.

Recently, several intratumoral therapies have been explored, either in combination or alone, with a goal of demonstrating that an '*in situ*' immunization strategy can yield systemic immune effects. For example, a retrospective analysis of the modified herpes virus, Talimogene laherparepvec, administered intratumorally, demonstrated an objective response rate of 26%,[14,15] with regression of some baseline uninjected lesions.[16] In the current phase II trial of Tavo, we used different response criteria, but regression of treated lesions was common. Overall, Tavo induced regression of at least one uninjected lesion in nearly half of patients, demonstrating clinical evidence of systemic antitumor immunity. In addition, a major benefit of the plasmid electroporation platform is that it can be modified relatively easily, based on translational data, to create next-generation therapies. Indeed, preclinical testing of a next-generation plasmid that induces expression of IL-12, CXCL9, and tumor membrane-anchored anti-CD3 is ongoing.[17]

Intratumoral Tavo electroporation was well tolerated, and it did not induce the systemic symptoms associated with intravenous cytokine administration and even constitutional symptoms were mild and infrequent. No grade 4 adverse effects were noted, and only six patients had grade 3 adverse effects (local pain, five patients and cellulitis, one patient). While systemic cytokine administration induces fever, chills, and pyrexia suggesting a systemic inflammatory response, despite a high rate of regression of untreated lesions, these symptoms were not observed in patients treated with Tavo.

Intratumoral IL-12, as generated by Tavo, induces cDC1 and establishes DC-T cell crosstalk that mediates tumor rejection.[18] Since cDC1 play a crucial role in recruiting and activating CD8+ T cells into the tumor microenvironment[10,11,18] and are in turn induced by NK cells,[18] we explored the effect of Tavo, in this publication, in a study by Garris et al.,[19] and in combination with PD-1 (manuscript submitted for review). Tavo induces activation across multiple classes of immune transcripts (Figure 4), including immune activation (Figure 4B), NK cell (Figure 4C), and antigen presentation (Figure 4D). The immune activation produced by Tavo results in both increased inflammatory gene expression, including expression of IFN-γ associated genes, and adaptive immune resistance, with increased expression of PD-L1 and TGFβ. This induction of adaptive resistance through PD-1/PD-L1 could explain the high proportion of responses to subsequent PD-1 blockade in patients progressing on Tavo (Figure 3B). Based on these findings, patients have now been treated on two prospective phase II clinical trials of Tavo in combination with the anti-PD-1 antibody pembrolizumab. A study of patients with few partially exhausted ($PD1^{hi}CTLA\text{-}4^{hi}CD8^{+}$) cells has been completed and results will be reported elsewhere (submitted for publication) and a larger single-arm study in patients with documented progression on PD-1 blockade (KEYNOTE-695) is currently ongoing.

In summary, Tavo treatment drives changes in the immune microenvironment resulting in both local and global immune responses with minimal systemic toxicity. Our data demonstrate that this *in situ* tumor vaccination strategy can be a safe and effective approach to inducing multiple sustained, productive changes in the immune microenvironment that would be too toxic using similar systemic agents.

FUNDING

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DISCLOSURE

AA is a paid advisor to OncoSec Medical, Inc. and he holds stock options in the company. He is also a paid advisor to Array, Regeneron, and Valitor. He also receives research funding from Acerta, Amgen, AstraZeneca, BMS, Dynavax, Genentech, Idera, Incyte, Idera, ISA, LOXO, Merck, Novartis, Regeneron, Sensei, and Tessa. He previously received research funding from Amgen, Celldex, GlaxoSmithKline, Lilly, Medimmune, Plexxicon, Roche, OncoSec Medical, Inc. SB, research funding from OncoSec Inc and Merck Inc. SA, research funding from OncoSec Inc. and Merck Inc. KL receives research funding from OncoSec Inc. and Merck Inc. MF receives research funding from OncoSec Inc; Advisor Boards of Novartis, Pulse Bioscience, Array Bioscience, Bristol Myers Squibb, Sanofi. LF receives research funding from OncoSec, Merck, AbbVie, Bavarian Nordic, BMS, Dendreon, Janssen, Roche/Genentech. CBB is advisor to PrimeVax, BMS. Stock ownership in BMS, Patent US20180322632A1: image processing systems and methods for displaying multiple images of a biological specimen. DB is an employee of OncoSec Medical, Inc. RT is an employee

of OncoSec Medical, Inc. EB is an employee of OncoSec Medical, Inc. MHL is a former employee of OncoSec Medical, Inc. Consulting: Immunomic Therapeutics, Inc., Pulse Biosciences, Inc., Juno Therapeutics, Inc., Genexine, Inc., NKarta Therapeutics, Inc., Seattle Genetics, Inc., Ideaya Biosciences, Inc., Apros Therapeutics, Inc., IgM Biosciences, Inc., Immune Design Corporation, Plexxikon, Inc., Curis, Inc. She is married to RHP. with conflict listed next. RHP is a former employee of OncoSec Medical, Inc. with equity. He also has consulting income from Immunomic Therapeutics, Inc., Pulse Biosciences, Sensei Biotherapeutics, AbbVie, Calithera Biosciences, Minerva Biosciences, AstraZeneca, Curis, Inc. He has received research funding from Exicure Therapeutics, X4-Pharma, Incyte Pharmaceuticals. He is married to MHL with conflicts listed earlier. SG is a former employee of OncoSec Medical, Inc., currently employed by Alloplex Biotherapeutics, Inc. KKT receives research funding from OncoSec, Merck Inc., Takeda, and Regeneron; consulting for Compugen, Pulse Biosciences. CT is an employee of OncoSec Medical, Inc. with equity. AD receives research funding from OncoSec Inc., Merck, BMS, Pfizer, Novartis, Roche/Genentech, Xencor, Consultant for Incyte, Novartis, Amgen, Caris Inc. All other authors have declared no conflicts of interest.

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